HORMONE REPLACEMENT FOR PREVENTION AND TREATMENT OF OSTEOPOROSIS:
What are the Options?

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INTRODUCTION

Osteoporosis has been defined as a condition characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in bone fragility and susceptibility to fracture (1). Hence the most important clinical sequel is fracture, a source of significant pain, disability and health care costs.

Using the World Health Organization working party definition for osteoporosis (a bone mineral density (BMD) more than 2.5 standard deviations below the mean for young healthy adult women at any site), it has been estimated that 30% of all postmenopausal women have osteoporosis (2). For many years hormone replacement therapy has been recognised as the first choice of treatment for osteoporosis, but more recently a number of alternatives have become available. This chapter will review the current evidence for the use of HRT in both prevention and treatment of osteoporosis as well as its relative efficacy in comparison to newer agents.

ESTROGEN AND BONE

Normal bone is not quiescent, but constantly undergoing remodelling characterised by a sequence of resorption, followed by new matrix formation.
and mineralization to allow fine control of calcium homeostasis and meet its other function of skeletal support. This process involves the 'coupling' of osteoclastic bone resorption and subsequent osteoblastic activity as a discrete bone remodelling unit (3). At any one time, there is a proportion of bone which has been resorbed but not yet 'rebuilt'. This is termed the remodelling space.

In estrogen deficiency states, there appears to be an increased rate of activation of bone remodelling units, and hence a larger remodelling space. An increase in osteoclast activity causes deeper resorptive spaces. Such an increase in bone resorption, compounded by a degree of impairment in osteoblast function, results in 'uncoupling' of the remodelling process and a net loss in bone substance. As resorptive spaces become larger and are inadequately refilled, the risk is of perforation of bony trabeculae and permanent loss of architectural elements (4). This in turn causes further deterioration in inherent bone strength.

At the menopause, overall bone turnover is increased with resorption exceeding formation, resulting in a negative calcium balance of about 100mg per day (5). Oestrogen replacement reverses these changes (6). An early rapid increase in bone mass is seen with treatment, which corresponds to the filling in of the remodelling space.

The mechanism of action of estrogen on bone is not clear. Estrogen receptors have been identified on osteoblasts and osteoclasts (7), and on marrow stromal cells. Estrogen acts directly on osteoclasts to cause a decrease in resorption activity in vitro (8). Its action on other cell lines is not clear.

The effects of estrogen deficiency on bone are mediated by cytokines released in the local bone marrow environment (9). It has been shown that interleukin-1 (IL-1) and tumour necrosis factor (TNF) activate osteoclasts in the initial phase of rapid bone loss seen post-ovariectomy (10-12). The later phase of slower bone resorption is mediated by IL-1, TNF-α and interleukin-6 (IL-6), which together stimulate osteoclastogenesis. IL-1 and TNF-α also have a positive feedback effect on IL-6 (13). Studies using transgenic mice expressing high blood levels of a soluble TNF receptor type I fusion protein, which neutralizes TNF-α, showed protection against the post-ovariectomy bone loss seen in controls (11). Although there is evidence of a complex interplay between cytokines in bone remodelling, this would suggest that suppression of TNF-α alone is required to prevent bone loss associated with estrogen deficiency.